



AMD3100/CXCR4 inhibitor

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The original bicyclam, JM1657 (JM standing for Johnson Matthey) was discovered as a contaminant in a commercial preparation of monocyclams when evaluated for their anti-HIV activity. The original compound, in which the cyclam rings were tethered by a C–C linkage could not be re-synthesized but launched the synthesis of new bicyclams in which the cyclam moieties were linked through an aliphatic bridge: one of these derivatives, i.e., JM2763, exhibited an anti-HIV activity similar to that of JM1657 (1). The compound was postulated to

interfere with the uncoating of HIV, a stage in the replicative cycle of HIV, which was (and still is) ill-defined. A quantum jump in anti-HIV potency was achieved with the synthesis of AMD3100 (AMD standing for AnorMeD) (which was originally called JM3100), where the two cyclam rings are tethered by an aromatic bridge (**Figure 1A**) (2). The compound was active against HIV in the low nanomolar concentration range and generated considerable commercial interest, although its precise mechanism of action remained enigmatic (3, 4). Finally,

the viral glycoprotein gp120 was identified as the molecular target of AMD3100 (5). It appeared to be an indirect target. The direct target was CXCR4, with which gp120 has to interact for HIV to enter the cells. AMD3100 was shown to specifically antagonize CXCR4, and thus to block the entry of the T-lymphotropic HIV strains (6–8). AMD3100 appears to be a highly specific inhibitor of CXCR4 (9): it only blocks, as measured by the Ca^{++} flux, the signal pathway from CXCR4 (**Figure 1B**) and not that of any other receptor for either CXCR4 or

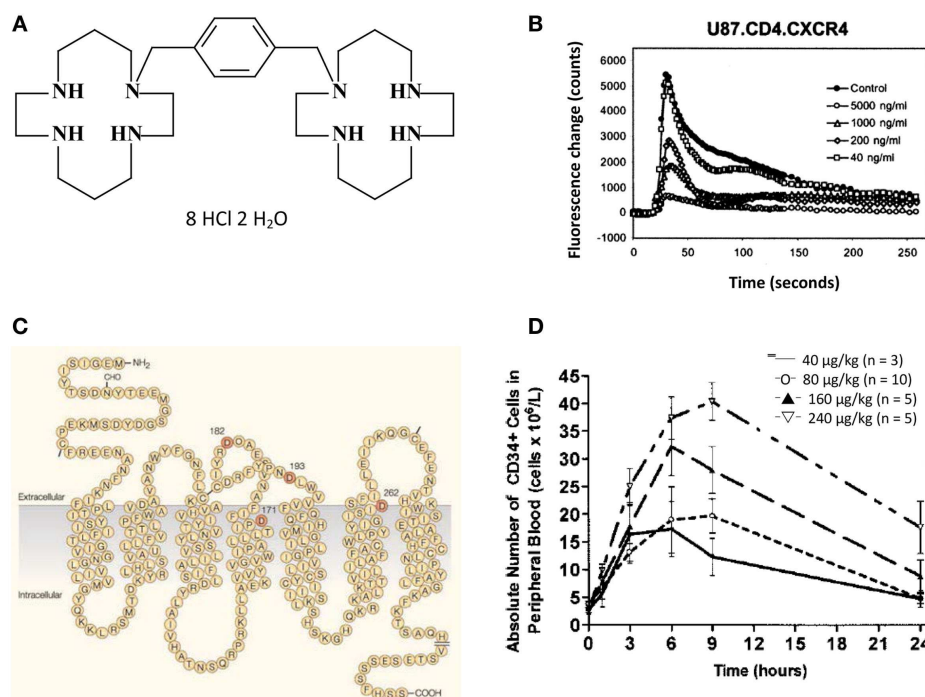


FIGURE 1 | (A) Structure of AMD3100. **(B)** Inhibitory effect of AMD3100 on Ca^{++} flux in CXCR4 transfected cells (9). **(C)** The CXCR4 receptor. Crucial aspartic acid residues at positions 171, 182, 193, and

262 in the interaction of CXCR4 with AMD3100 are indicated (11). **(D)** Mobilization of CD34⁺ hematopoietic stem cells (HSCs) by AMD3100 (12).

C–C-chemokines (9). Certain aspartic acid residues play an essential role in the interaction of CXCR4 with AMD3100 (**Figure 1C**) (10, 11).

Within the scope of the potential clinical use of AMD3100 for the treatment of HIV infections, initial phase 1 clinical trials were initiated (13). These studies revealed an increase in the white blood cell (WBC) counts peaking at about 8–10 h after (subcutaneous) injection. These WBCs contained hematopoietic stem cells (HSCs) carrying the CD34 marker (12) (**Figure 1D**). In fact, the first proof-of-principle that AMD3100 could mobilize hematopoietic stem and progenitor cells was provided by Broxmeyer et al. (14). Thus, the concept was born that AMD3100 (now also called plerixafor or Mozobil®) could function as a mobilizer of HSCs. This mobilization is clearly based on the interaction of AMD3100 with CXCR4. CXCR4 is normally the receptor for the chemokine SDF-1 (now called CXCL12), which is responsible for the “homing” of the HSCs in the bone marrow. Under the influence of AMD3100, the HSCs leave the bone marrow to enter the bloodstream where they can be collected and subsequently used for autologous transplantation. In December 2008, Mozobil® was approved by the FDA for this indication in patients with non-Hodgkin's lymphoma or multiple myeloma. It is used in combination with granulocyte-colony stimulating factor (G-CSF) [for review, see Keating (15)]. For prescribing information, see Ref. (16).

AMD3100 was not further developed for the treatment of HIV infections essentially because of two reasons: (i) AMD3100 was not effective against the M-tropic CCR5 HIV strains, a problem that could be circumvented by the concomitant (oral) use of a CCR5 antagonist, maraviroc (Selzentry®), and (ii) it had to be injected subcutaneously, as it was not orally bioavailable. Subcutaneous injection is indeed a problem for long-term administration, and Fuzeon® (enfuvirtide) is the only anti-HIV drug out of more than 25, which has to be administered by injection, and, therefore, not widely used. Attempts to increase the spectrum of AMD3100 derivatives toward M-tropic HIV strains and, particularly, to increase their oral bioavailability led to the synthesis of AMD3465 (17), AMD11070 (18),

and various other compounds (19–21), which, however, were not further developed as clinical candidates for treatment of HIV infections. Related CXCR4 antagonists such as KRH-1636 (22), KRH-3955 (23), and T140 analogs (24) were described by Naoki Yamamoto and his colleagues in Japan.

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